The natural history of egg allergy in an observational cohort

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Background: There are few studies on the natural history of egg allergy, and most are single-site and nonlongitudinal and have not identified early predictors of outcomes.
Objective: We sought to describe the natural course of egg allergy and to identify early prognostic markers.
Methods: Children age 3 to 15 months were enrolled in a multicenter observational study with either (1) a convincing history of an immediate allergic reaction to egg, milk, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis and a positive SPT response to egg or milk. Children enrolled with a clinical history of egg allergy were followed longitudinally, and resolution was established based on successful ingestion.
Results: The cohort with egg allergy consists of 213 children followed to a median age of 74 months. Egg allergy resolved in 105 (49.3%) children at a median age of 72 months. Factors that were most predictive of resolution included the following: initial reaction characteristics (isolated urticaria/angioedema vs other presentations), baseline egg-specific IgE level, egg SPT wheal size, atopic dermatitis severity, IgG_4 level, and IL-4 response (all $P < .05$). Numerous additional baseline clinical and demographic factors and laboratory assessments were not associated with resolution. Multivariate analysis identified baseline egg-specific IgE levels and initial reaction characteristics as strongly associated with resolution; a calculator to estimate resolution probabilities using these variables was established.
Conclusions: In this cohort of infants with egg allergy, approximately one half had resolved over 74 months of follow-up. Baseline egg-specific IgE levels and initial reaction characteristics were important predictors of the likelihood of resolution. (J Allergy Clin Immunol 2014;133:492-9.)

Key words: *Egg allergy, natural history, food allergy, IgE*

Allergy to egg is estimated to affect 0.5% to 2.5% of young children,[1-4] with a recent estimate of up to 8.9% of infants reacting to raw egg in one study from Australia.[5] Having an egg allergy or being sensitized to egg is associated with increased

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Supported by National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) grant U19AI066738 and U01AI066560. The project was also supported by grants UL1 TR-000154 (National Jewish), UL1 TR-000067 (Mount Sinai), UL1 TR-000039 (Arkansas), UL1 TR-000083 (University of North Carolina) and UL1 TR-000424 (Johns Hopkins) from the National Center for Research Resources (NCRR), a component of the NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Disclosure of potential conflict of interest: S. H. Sicherer has received research support from the National Institute of Allergy and Infectious Disease (NIAID), is a board member for the American Board of Allergy and Immunology, has consultant arrangements with Novartis and Food Allergy Research and Education, and receives royalties from UpToDate. R. A. Wood has consultant arrangements with the Asthma and Allergy Foundation of America, is employed by Johns Hopkins University, has received research support from the National Institutes of Health (NIH), and receives royalties from UpToDate. B. P. Vickery has received research and travel support from the NIH/NIAID. S. M. Jones is on the Medical Advisory Board for Food Allergy Research & Education; is a National Advisory Board member for St Louis Children's Hospital Food Allergy Management and Education; has consulted for the Gerson Lehrman Group; has received research support from the NIH, Food Allergy Research & Education, and the National Peanut Board; has a pending grant from the Department of Defense; has received payment for lectures from Abbott Nutrition International, the Kentucky Society for Allergy, Asthma & Immunology, the New England Allergy Society, the American College of Allergy, Asthma & Immunology, Indiana University Medical School and Riley Children's Hospital, the Spanish Society of Allergy & Clinical Immunology, the Oregon Allergy, Asthma & Immunology Society, and the European Academy of Allergology and Clinical Immunology; has received payment for manuscript preparation from the American Academy of Allergy, Asthma & Immunology; and is on the Arkansas Medicaid Drug Review Committee. D. M. Fleischer has received research support from the NIH/NIAID and Monsanto, has consultant arrangements with Sanofi-Aventis, is employed by National Jewish Health, receives royalties from UpToDate, and has received payment for the development of educational presentations from the American Academy of Pediatrics Symposium 2013. P. Dawson has received research support from the NIH. A. W. Burks has received research support from the NIH, the Wallace Research Foundation, and Hycor Biomedical; has board memberships with the Academy of Allergy, Asthma & Immunology, the Hypersensitivity, Autoimmune, and Immune-mediated Diseases Study Section of the NIH, the Food and Drug Administration Food Advisory committee, the Food Allergy & Anaphylaxis Network Research Advisory Board, and the Merck US Allergy Immunotherapy Allergist Advisory Board; has consultant arrangements with Dow AgroSciences, McNeill Nutritionals, Merck, Novartis Pharma AG, Sanofi Aventis US, Schering Plough, Unilever, ExploraMed Development, GLG Research, and Regeneron Pharmaceuticals; is employed by UNC Children's Hospital; has a pending grant from Food Allergy Research and Education; has received payment for lectures from Abbott Laboratories, Mylan Specialty, and the American College of Allergy, Asthma & Immunology; has various US patents related to peanut allergens and methods; has received payment for development of educational presentations from Current Views 2012; and is a minority stockholder in Allertein and Mastcell Pharmaceuticals. A. Grishin has consultant arrangements with Allertein Therapeutics. D. Stablein has received research support from the NIH. H. A. Sampson has received research support from the NIAID, the NIH, and Food Allergy Research Education; is Chair of the PhARF Award review committee; has consultant arrangements with Allertein Therapeutics, Regeneron, and the Danone Research Institute; has received payment for lectures from Thermo Fisher Scientific, UCB, and Pfizer. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 28, 2013; revised November 1, 2013; accepted for publication December 6, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.12.1041

Abbreviations used
AD: Atopic dermatitis
CoFAR: Consortium of Food Allergy Research
Ct: Cycle threshold
HR: Hazard ratio
OFC: Oral food challenge
SPT: Skin prick test

risk of peanut and other food allergies, atopic dermatitis (AD), and development of respiratory allergies and asthma.[6-9] For those with egg allergy, avoidance is difficult, and allergic reactions from accidental ingestion are common.[10] Fortunately, egg allergy typically resolves during childhood.[11-14] However, the rate of resolution might be slowing, with a past study suggesting the majority are egg tolerant by age 3 years[13] and a recent study suggesting about half of children reach tolerance by age 12 years.[11] The recent study from a referral population showed persistent egg allergy for 42% of children in late adolescence,[11] suggesting the number of adults with egg allergy might increase with time, although the current estimate of egg allergy among adults is 0.2%.[9] The ability to determine the prognosis of egg allergy is critical because potential interventions under study carry risks[15] and ideally would be applied in those unlikely to achieve resolution naturally.

The Consortium of Food Allergy Research (CoFAR) enrolled 512 infants with likely egg or milk allergy but without previously known peanut allergy in a multicenter observational study to address the immunologic, genetic, and environmental factors that affect the natural course of food allergy.[16,17] Evaluations were offered every 6 months, and oral food challenges (OFCs) were offered as clinically indicated, similarly to the studies described above.[11-14] We previously reported the natural course of milk allergy in this cohort and identified a number of prognostic markers that could be used to estimate resolution rates using baseline characteristics.[18] The primary aim of the current analysis is to assess the natural history of egg allergy in the infants enrolled in this cohort, with a focus on the clinical factors predicting the resolution of egg allergy over the first 6 years of life.

METHODS

Subjects, study definitions, and procedures

The subjects of this study are a subset with egg allergy of a larger cohort of 512 infants originally enrolled at 3 to 15 months of age at 5 sites (children with egg allergy/total enrolled per site): the Icahn School of Medicine at Mount Sinai, New York (47/106); Duke University Medical Center, Durham, North Carolina (now followed at the University of North Carolina, 20/103); Johns Hopkins University School of Medicine, Baltimore, Maryland (37/109); National Jewish Health, Denver, Colorado (42/99); and Arkansas Children's Hospital, Little Rock, Arkansas (67/95), as described previously.[16,18] Enrollment criteria for the whole cohort were designed to include atopic children with likely egg or milk allergy at risk of peanut allergy but without current peanut allergy. Briefly, enrollment required either (1) a history of a convincing immediate allergic reaction to egg, cow's milk, or both and a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe AD and a positive SPT response to egg, milk, or both. Exclusion criteria included clinical evidence of peanut allergy or a peanut-specific IgE level of greater than 5 kU_A/L identified before enrollment.[16,18]

The subgroup of children in the current study had a diagnosis of egg allergy at the time of enrollment or acquired this diagnosis after enrollment with no prior evidence of egg tolerance. Study procedures were reviewed and approved by the National Institutes of Allergy and Infectious Diseases Data Safety Monitoring Board and by local institutional review boards, and written signed consent forms were obtained.

Participants were considered to have egg allergy if their initial reaction was either (1) a positive physician-supervised OFC result; (2) a convincing reaction (defined by symptoms within an hour of isolated ingestion that included at least urticaria and/or angioedema, difficulty breathing, wheezing, throat tightness, and/or vomiting) and sensitization to egg (egg-specific IgE $\geq$0.35 kU_A/L and/or SPT response >3 mm); or (3) a flare of AD associated with egg ingestion and an egg-specific IgE level of greater than 2 kU_A/L, a level that is greater than 95% predictive of egg allergy in infants.[13] Reaction details were recorded regarding skin, oral, respiratory, gastrointestinal, and cardiovascular symptoms. The study analyzed 3 mutually exclusive initial clinical presentations of reaction to egg ingestion: AD diagnosis (flare of AD), skin-only reactions (acute hives and/or angioedema), or systemic reactions (eg, more than isolated skin reactions, including respiratory and gastrointestinal reactions). Subjects were considered egg tolerant if they ingested whole concentrated egg products (scrambled egg or French toast) in serving size quantities without symptoms either during physician-supervised OFCs or after introduction at home. Dietary ingestion of products with extensively heated egg (baked egg, for example as an ingredient in a muffin or cookie) was queried but was not considered evidence of resolved egg allergy.

Dietary, medical, and social histories were obtained by using questionnaires completed during enrollment interviews. A diagnosis of asthma and allergic rhinitis was based on parental report or parental report of a physician's diagnosis. A diagnosis of other food allergies included per-protocol definitions for egg and peanut,[16,18] whereas for other foods, this was based on a clinical diagnosis by a study physician.

Diagnosis of baseline AD, in distinction to the AD flares caused by egg ingestion described above, required pruritus and an eczematous rash (acute, subacute, or chronic) with typical morphology and age-specific patterns, a chronic or relapsing history, atopy (personal and/or family history or IgE reactivity), and xerosis. AD severity was graded based on criteria previously described and published by Rajka and Langeland.[19] Briefly, the AD severity was graded as mild, moderate, or severe (see Table E1 in this article's Online Repository at www.jacionline.org), as described previously.[18] Atopic disease history in parents of the enrolled infants was based on previously published definitions and was recorded by parental report.[20]

To maintain uniformity and an observational approach, the study design includes evaluations, care for food allergy, and instructions on dietary management that were uniform among the clinical centers and reflect practice parameters in force at the time of enrollment for AD,[21] food allergy,[22] and allergy prevention.[23] Participants were evaluated in person at enrollment, 6 months, 12 months, and yearly thereafter, with additional telephone follow-up between each visit and instructions to contact the study site for any allergic reactions, at which time additional details were obtained.[10] OFCs to egg were typically offered when egg-specific IgE serum concentrations were less than 2 kU_A/L and the mean skin test wheal diameter was less than 10 mm if there was no reaction in the preceding 6 months. However, OFCs were not withheld if additional clinical data warranted OFCs outside of these parameters (eg, tolerance of a small accidental exposure or parental preference). OFC results were considered positive for persistent subjective or objective symptoms.[24] OFCs were performed with cooked whole or pasteurized powdered egg but not raw egg white.

SPTs

SPTs were performed by using the GreerPick (Greer Laboratories, Lenoir, NC), with participants avoiding antihistamines for at least 5 half-lives of the specific agent. Tests were performed on the infant's back, and at 15 minutes, the wheal was outlined in pen and transferred by tape to paper. The sizes of the longest diameter and its longest perpendicular were averaged. An SPT score was computed by subtracting the saline control measure, and a positive SPT response is defined by a score of 3 mm or greater. Tests were considered reliable if the wheal size of the negative control (50% glycerin-saline) was 3 mm or smaller and the wheal size of the histamine control was at least 3 mm larger than the wheal size of the negative control. All sites used the same lot of

reagents, and training was performed to ensure consistency. The egg (chicken) white extract was obtained from Greer Laboratories (catalog no. F272).

Serum egg-specific IgE and IgG_4 levels

The concentration of specific IgE antibody to egg white was measured from plasma at a central laboratory (Mount Sinai) by using the Thermo Fisher ImmunoCAP system (Thermo Fisher, Uppsala, Sweden) and reported in kilounits of antigen per liter. A level of greater than 0.35 kU_A/L was considered positive. The concentration of IgG_4 antibodies to milk were also measured from plasma samples by using the ImmunoCAP system (detection limit, 0.07 mg/L).

Mononuclear cell stimulation and PCR analysis

Studies were performed to determine whether egg-specific T_H2 or regulatory T-cell gene expression was predictive of egg allergy outcomes. PBMC isolation was performed by using Ficoll-Paque density gradient centrifugation, and cultures were performed at each clinical site on fresh venous blood samples, as previously described.[16] Briefly, 4 million cells per condition were cultured for 48 hours in AIM-V serum-free media (Invitrogen, Carlsbad, Calif) with egg white protein (50 μg each/mL), aqueous peanut extract (50 μg/mL), tetanus toxoid (5 μg/mL), and purified α-, β-, and κ-caseins (50 μg each/mL), and additional control stimulations were performed with medium alone (negative) and anti-CD3/anti-CD28 beads (positive). At the end of the culture period, cells expressing CD25 were enriched by means of selection with anti-CD25–coated paramagnetic beads, according to the manufacturer's protocol (Miltenyi Biotech, Bergisch Gladbach, Germany). Pilot experiments demonstrated approximately 10-fold enrichment of $CD25^+$ cells, with 70% to 80% of selected cells coexpressing CD3, CD4, and CD25, as measured by means of flow cytometry. The entire selected fraction of cells was immediately lysed in RLT buffer (Qiagen, Hilden, Germany) and stored at −80°C until RNA purification. The quantitative PCR was carried out in the central laboratory according to the in-house established protocol by using SYBR Green I fluorescence detection in a 384-well plate on ABI 7900 (Applied Biosystems, Foster City, Calif). Raw PCR analysis and annotation were performed on coded samples. The cycle threshold (Ct) number was set by software with confirmation and adjustment as necessary to define the threshold of linear amplification. For the gene expression data, ΔΔCt was calculated by subtracting the *RPS9* reporter gene Ct and then normalizing by subtracting the standardized medium control response. Negative values indicate relatively higher activity, with a unit score change corresponding to a doubling. Nondetected genes were arbitrarily assigned a Ct of 40.

Statistical analysis

Time to resolution of egg allergy was measured with age as the time metric whether enrolled with egg allergy or having the diagnosis after enrollment. Although the time of allergy diagnosis varied depending on when food introduction and diagnostic testing were performed, each subject's first definitive diagnosis was positive for egg allergy. Proportional hazards regression models were fit to examine covariates for their effect on the hazard or risk function.[25] The estimated survival distribution was calculated from the relative hazard, which is the exponentiated sum of the linear combination of the products of the parameter estimates with their respective clinical characteristics. The common underlying empiric cumulative hazard function Lambda(t) is estimated with a step function, and the resolution curve is estimated as follows:

$$1-\exp(-\mathrm{RH} * \mathrm{Lambda}[t]).$$

In this article hazard refers to the chance of a beneficial event (ie, allergy resolution), and variables are structured so that large relative hazard values are associated with increased chance of allergy resolution. A multivariate proportional hazards model was fit by using significant baseline factors from the univariate models to assess the probability of allergy resolution over time. The final model was selected based on factor significance and model fit. Time-varying clinical covariate analyses used the most recent available assessment in the model, and nonproportional hazards were examined by fitting linear and spline function interactions with time. Reported *P* values are 2-tailed when applicable, and SAS 9.2 (SAS Institute, Cary, NC) and R software were used for the computations.

TABLE I. Baseline characteristics

		Egg allergy resolved			
		No		Yes	
	All (no.)	No.	Percent	No.	Percent
Total subjects	213	108	50.70	105	49.30
Sex					
Female	63	26	41.27	37	58.73
Male	150	82	54.67	68	45.33
Race					
White	161	80	49.69	81	50.31
Black/African American	36	19	52.78	17	47.22
Asian	12	7	58.33	5	41.67
Other	4	2	50.00	2	50.00
Baseline egg IgE (kU_A/mL)*					
<2.0	78	30	38.46	48	61.54
≥2.0-10.0	72	35	48.61	37	51.39
≥10.0	60	41	68.33	19	31.67
Reaction class†					
AD diagnosis	27	17	62.96	10	37.04
Skin only	93	37	39.78	56	60.22
Other system	93	54	58.06	39	41.94
Egg SPT wheal (mm)‡					
<5	50	20	40.00	30	60.00
>5	162	87	53.70	75	46.29
Baseline age (mo)					
3-5	13	8	61.54	5	38.46
6-8	32	14	43.75	18	56.25
9-12	88	48	54.55	40	45.45
13-15	80	38	47.50	42	52.50
Baseline AD					
None	17	9	52.94	8	47.06
Mild	31	11	35.48	20	64.52
Moderate	104	52	50.00	52	50.00
Severe	61	36	59.02	25	40.98
Breast-feeding history					
Never	40	22	55.00	18	45.00
Yes, currently	57	29	50.88	28	49.12
Yes but no longer	116	57	49.14	59	50.86
Other food allergy					
No	103	49	47.57	54	52.43
Yes	110	59	53.64	51	46.36
Baseline milk allergy					
Allergic	91	48	52.75	43	47.25
Other	122	60	49.18	62	50.82
Asthma/rhinitis					
No	169	89	52.66	80	47.34
Yes	44	19	43.18	25	56.82

*Three participants had missing baseline egg-specific IgE values.
†The mutually exclusive clinical presentation of the initial reaction to egg ingestion was categorized as follows: AD diagnosis (flare of AD; this category included egg-specific IgE >2 kU_A/L), skin-only reactions (acute hives and/or angioedema), or systemic reactions (eg, more than isolated skin, including respiratory and gastrointestinal reactions).
‡One subject had missing baseline egg SPT values.

RESULTS

Of the 512 enrolled infants, the cohort with egg allergy consisted of 213 children, of whom 140 were given a diagnosis of egg allergy at baseline. In the remaining 73 children, the

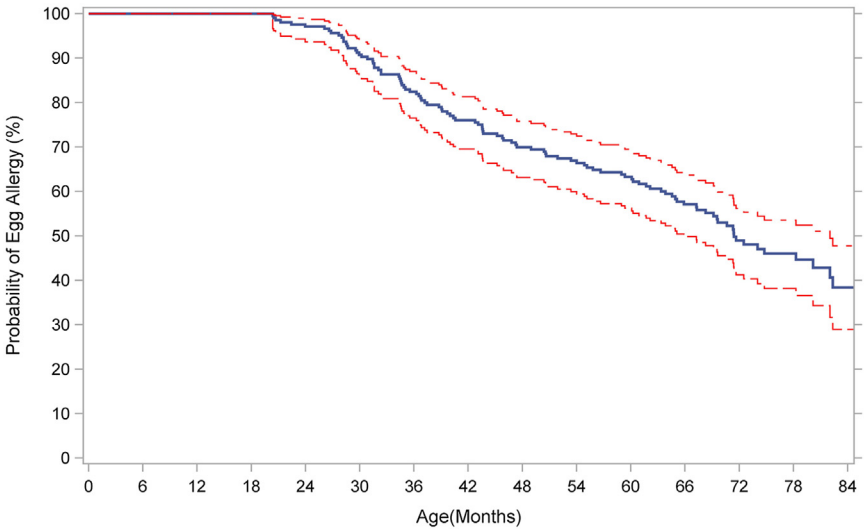

FIG 1. Kaplan-Meier analysis of egg allergy resolution over time with pointwise 95% CIs.

diagnosis was categorized as uncertain at the entry visit, but egg allergy was subsequently confirmed at a median age of 23.2 months (interquartile range, 16.1-41.9 months), 10 based on OFC results. Key baseline characteristics are summarized in Table I and Table E2 in this article's Online Repository at www.jacionline.org. AD was present in 196 and categorized as mild in 31, moderate in 104, and severe in 61. Twenty-seven (12.7%) infants were given diagnoses of egg allergy based on AD criteria, whereas the remainder had a history of an acute reaction and positive test results. Ninety-three subjects were first given a diagnosis based on a reaction or clinical history that was limited to skin symptoms (hives, pruritus, or swelling) after exposure. Another 93 subjects were given a diagnosis based on a reaction that involved more extensive symptoms (eg, oral, upper/lower respiratory, gastrointestinal, or cardiovascular) in addition to or apart from urticaria/angioedema.

One hundred five (49.3%) of the 213 participants have now resolved their egg allergy, with a median age of resolution of 72 months and a median age at last follow-up of 74 months (Fig 1). Resolution was defined based on OFC results in 47 (44.8%) and by successful home introduction of whole (not baked) egg products in the remainder recorded by the time of their visit. Regarding exposure to egg in baked goods, at the 6-year time point, 43 (38.1%) of 113 subjects with unresolved allergy reported tolerating at least some baked egg products, whereas 4 reported reactions to ingestion of baked egg products.

Additional baseline characteristics of the cohort, comparing those with and without egg allergy resolution, are presented in Table I, and Cox regression analyses are shown in Table II. The baseline characteristics that were most predictive of egg allergy resolution included egg-specific IgE levels and the characteristics of the presenting reaction. Specifically, highly significant differences ($P < .001$) in the rate of resolution were noted when comparing those subjects with baseline egg-specific IgE levels of less than 2 kU_A/L, 2 to 10 kU_A/L, and 10 kU_A/L or greater (Fig 2). Significant differences ($P = .007$) in resolution were also predicted by reaction classification, with those having acute reactions with only skin symptoms having a greater likelihood of resolution compared with those with acute reactions involving systems beyond the skin (Fig 3, distinguishing the 3 clinical categories described above). Those with an AD flare from egg and those with systemic reactions to egg had poorer prognosis than those with isolated urticaria/angioedema. The poor prognosis of the former reaction category might be partly influenced by the requirement for increased egg-specific IgE antibody levels in the definition of an egg-induced allergic reaction manifested by an AD flare. Resolution was also associated with baseline AD severity (Table II and see Fig E1 in this article's Online Repository at www.jacionline.org), egg SPT responses (Table II and see Fig E2 in this article's Online Repository at www.jacionline.org), and egg-specific IgG_4 levels (Table II and see Fig E3 in this article's Online Repository at www.jacionline.org), although only weakly. Only 18 (17.1%) of the subjects with resolved egg allergy reported no AD at the time of resolution.

Additional factors that correlated with rapidity of resolution included sex, T-cell responses (see below), and the egg-specific IgE/IgG_4 ratio (hazard ratio [HR], 0.62; 95% CI, 0.47-0.82; $P < .001$), although this latter effect appears to be a result of the strong correlation (Spearman $r = 0.63$) with egg-specific IgE levels. Parameters not associated with resolution included race, breast-feeding, other food allergies, baseline milk allergy diagnosis, asthma or rhinitis, family income, parental education, presence of siblings, and parental atopy. Although baseline milk allergy was not related to egg allergy resolution, when resolution of milk allergy was examined as a time-varying covariate, it was associated with egg allergy resolution, and the effect persisted when adjusted for log egg IgE levels and skin reaction classification (data not shown).

Not surprisingly, baked egg (eg, in muffins and cookies) consumption was related to resolution outcomes.[26] Egg allergy resolution rates were 75 (45.2%) of 166, 8 (57.1%) of 14, and 17 (70.8%) of 24 among the 204 subjects reporting no baked egg consumption, baked egg consumption with a reaction, and baked egg consumption without a reaction at the 6-month follow-up visit. The instantaneous risk ratios for resolution are 1.8 and 3.4 for the latter classes versus the nonconsumption group; the difference is statistically significant ($P < .001$) and is maintained after adjustment for log IgE levels and skin reaction classification. At 6 years of age, baseline characteristics,

TABLE II. Resolution of egg allergy (Cox regression analysis with 1 variable in the model at a time)

Risk factor for resolution of egg allergy	HR*	95% HR confidence limits	*P* value†
Baseline egg-specific IgE (kU_A/L)			
<2.0 vs ≥10	3.874	2.25-6.66	<.001
2-10 vs ≥10	2.064	1.19-3.59	
Baseline egg SPT wheal (mm)			
<5 vs ≥10	1.995	1.23-3.24	.002
5-<10 vs ≥10	0.860	0.55-1.35	
Baseline egg-specific IgG_4 (mg_A/L)			
<0.10 vs >0.4	1.991	1.19-3.32	.022
0.10-0.40 vs >0.4	1.346	0.78-2.33	
Baseline age (mo)			
3-5 vs 13-15	0.821	0.32-2.08	.782
6-8 vs 13-15	1.189	0.68-2.07	
9-12 vs 13-15	0.907	0.59-1.40	
Sex			
Female vs male	1.603	1.07-2.40	.022
Race			
White vs nonwhite	0.941	0.60-1.49	.795
Baseline AD			
None/mild vs moderate/severe	1.595	1.03-2.46	.036
Breast-feeding			
Yes but no longer vs never	0.811	0.48-1.38	.742
Yes, currently vs never	0.846	0.47-1.53	
Other food allergy			
Yes vs no	0.737	0.50-1.08	.119
Asthma or rhinitis			
Yes vs no	1.232	0.79-1.93	.364
Reaction class			
Skin only vs systemic	1.862	1.23-2.82	.007
AD diagnosis vs systemic	0.961	0.48-1.93	

*An HR of greater than 1 indicates a proportional increase in the chance of resolution of egg allergy.
†*P* values represent comparison of all variables in that category.

including reaction characteristics and egg-specific IgE levels, did not predict those who would go on to ingest products with egg baked into them.

T-cell studies were assessed at baseline for relationships of egg allergy resolution to antigen and control stimulated expression of mRNA for CISH, forkhead box protein 3 (FOXP3), GATA3, T-bet, IL-10, IL-4, and/or IFN-γ.[16] Genes that were associated with egg allergy resolution (lower expression of these genes was associated with a greater chance of resolution) include *IL4* stimulated by egg white (HR, 1.04; $P = .047$; see Fig E4 in this article's Online Repository at www.jacionline.org), peanut (HR, 1.05; $P = .037$), tetanus (HR, 1.06; $P = .005$), and casein (HR, 1.06; $P = .005$) and *FOXP3* stimulated by casein (HR, 1.05; $P = .046$). In adding egg-stimulated *IL4* expression to the variables in the clinical resolution model (described below), the HR was 1.04 ($P = .06$). Results for tetanus-stimulated (HR, 1.05; $P = .024$) and casein-stimulated (HR, 1.05; $P = .01$) *IL4* remained significant when added to the clinical model but added little additional predictive information.

Finally, we used the 2 baseline factors most predictive of egg allergy resolution to develop a composite score that could be applied to individual patients (see Table E3 in this article's Online Repository at www.jacionline.org). For example, as represented in Fig E5 in this article's Online Repository at www.jacionline.org, the likelihood of egg allergy resolution for 5 individual patients is predicted by using a composite index incorporating their egg-specific IgE levels and reaction classifications. An interaction between time and baseline egg IgE levels is observed, such that the predictive utility of baseline egg-specific IgE measurement decreases at later time points. We have provided a Web-based calculator based on our data, which is available for use in validation studies in other centers (see www.cofargroup.org).

DISCUSSION

Here we describe the natural history of egg allergy in a cohort of children enrolled in an observational study with a diagnosis of egg allergy. We found a resolution rate of almost 50% through age 6 years, which was similar to but slightly slower than the resolution rate of milk allergy in this cohort, which was approximately 50% by age 5 years.[18] This result appears to be slightly less favorable than that reported in 58 children by Boyano-Martinez et al,[13] who found resolution rates of 50% by age 4 to 4.5 years and 66% by age 7 years in children referred with food allergy, 50% of whom had AD. Other studies report early childhood resolution rates from 31% to 51%, but none are comparable because of different ages at presentation, referral bases, and length of follow-up.[12,14,27,28] In a population referred to a tertiary care center reported by Savage et al,[11] of 881 children, resolution by age 4 years was noted in only 4%, and by age 8 years, it was 26%, which is worse than observed in the present cohort. Studies of egg (and milk) allergy resolution rates clearly vary by population, with referral populations showing slower resolution rates than less selected groups.[12,29] The specific predictors of egg allergy resolution were different from those we observed with milk in this same cohort (eg, differences in influence of AD severity and gene expression profiles),[18] which adds to additional previous observations regarding the uniqueness of egg allergy and sensitization compared with milk. For example, egg allergy is a stronger early indicator of future allergic reactivity,[30] shows different gene expression profiles for allergic infants,[16] and has a higher likelihood to induce anaphylaxis in baked foods[31] compared with milk.

Few studies have attempted to identify early prognostic markers of egg allergy resolution, particularly prospectively. We identified a number of baseline factors that were associated with egg allergy resolution, but in the multivariate analysis the characteristics of the presenting reaction and the egg-specific IgE levels were by far the strongest indicators associated with resolution. Similar to our study, a prospective study of 58 children in one center identified several factors associated with egg allergy resolution in multivariate analysis, including symptoms at the time of the reaction (strongest predictor) and egg-specific IgE levels.[13] Severity of the initial reaction was also noted to relate to prognosis by Ford and Taylor.[14] In a retrospective chart review analysis, Savage et al[11] identified the highest recorded egg-specific IgE level, presence of other atopic disease, and other food allergies as predictive factors affecting resolution. These and other studies[32] suggest, like ours, that increased egg-specific IgE levels are strongly related to persistent egg allergy, a general concept that we also recently reported for milk allergy.[18]

Several additional factors that we identified as related to the natural course of egg allergy have been noted to be related to current/persistent egg allergy in a number of studies, including egg-specific IgE/IgG_4 ratios[33] and tolerance of egg in baked goods.[26,34] Regarding egg-specific IgG_4 levels, we might have

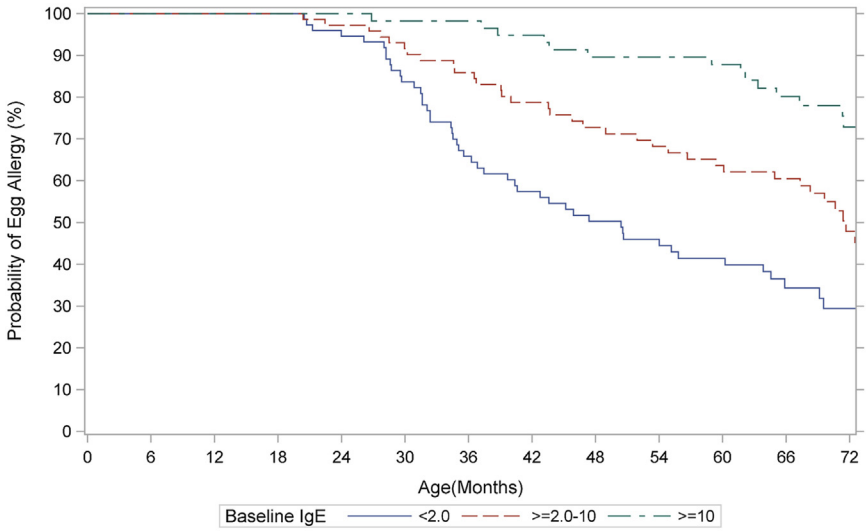

FIG 2. Kaplan-Meier analysis representing the relationship of egg allergy resolution to baseline egg-specific IgE levels. Individual curves represent IgE levels of less than 2 kU_A/L *(blue)*, 2 to 10 kU_A/L *(red)*, and 10 kU_A/L or greater *(green)*.

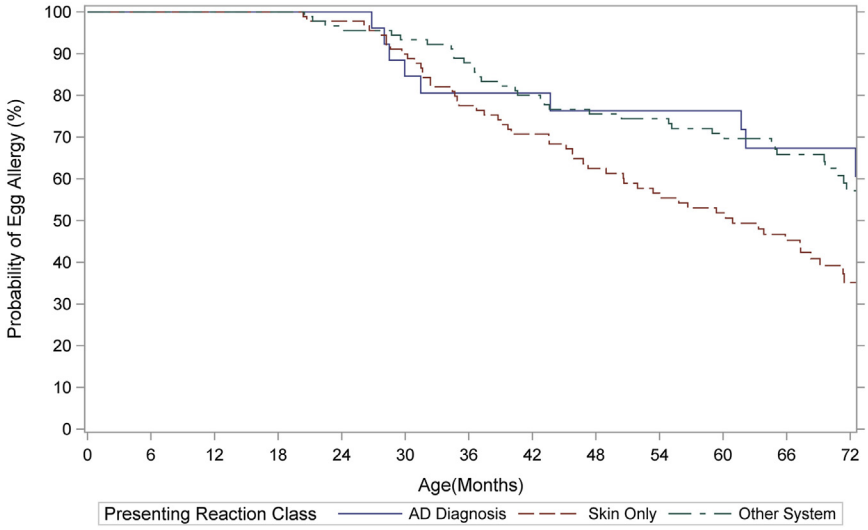

FIG 3. Kaplan-Meier analysis representing the relationship of egg allergy resolution to clinical presentation of initial reactions to egg. The mutually exclusive clinical presentation of the initial reaction to egg ingestion was categorized as the following: AD diagnosis (flare of AD; this category included egg-specific IgE >2 kU_A/L), skin-only reactions (acute hives and/or angioedema), or systemic reactions (eg, more than isolated skin, including respiratory and gastrointestinal reactions).

expected higher IgG_4 levels to predict resolution, as observed in immunotherapy treatment trials,[15] but we saw the opposite, which might indicate a difference in mechanisms between natural tolerance and desensitization induced by immunotherapy. Egg-specific IgG_4 levels increase with exposure, and the lower values in those who later had tolerance could simply reflect earlier careful avoidance of larger exposures. Nonetheless, the relationship of IgG_4 levels to outcomes was weak and not significant in multivariate analysis. Regarding ingestion of baked egg, we did not mandate exposure in this observational study and did not begin to monitor baked egg ingestion until after baseline visits. Although eventual ingestion of baked egg was associated with resolution, this outcome could reflect a milder phenotype prone to resolution, an immunotherapeutic benefit, or a phenomenon related to accelerated testing with whole-egg exposure after successful ingestion of baked egg. The distinctions are not evaluable in the present study design. Interestingly, among those with persistent allergy, exposure to baked egg products was not predicted by baseline characteristics.

T-cell stimulation studies identified several markers associated with the natural course of egg allergy in our cohort. We found reduced expression of egg-specific *IL4* mRNA to be associated with resolution, which is consistent with a prior report.[35] The subgroup evaluated here (those with egg allergy evaluated prospectively for resolution) are distinct from the entire cohort in which we reported no IL-4 signal, distinguishing those with

or without baseline egg allergy/sensitization,[16] which might account for the different results. Nonetheless, the IL-4 signal *P* value was marginal and not a strong contributor to the predictive models. However, a number of IL-4 responses to other stimulants were also associated with egg allergy prognosis, possibly reflecting a more generalized immune reactivity as a marker of resolution. Ultimately, these cellular studies did not contribute substantially to predicting outcomes.

Overall, our study has identified a number of factors that predict egg allergy outcomes, confirming a number of factors identified previously and uniquely providing the opportunity to use our large multicenter cohort to evaluate the most relevant baseline factors. The substantial predictive capacity of egg-specific IgE levels and clinical presentation allowed for the development of a novel algorithm to estimate the natural course of egg allergy. This composite index has been developed into an equation that can be applied to young (<15 months) patients presenting to the clinic and has been provided as a Web-based calculator, as well as a computer application (www.cofargroup.org). This unique tool might benefit health care providers and patients in providing early guidance as to the likelihood for disease resolution or persistence, but the utility of the calculator, although developed in a diverse clinical cohort, will need to be validated in other settings.

The strengths of this study include the sample size, the prospective design with re-evaluation at regular intervals, the inclusion of multiple research sites, and the exceptional follow-up rate. In addition, this study was the first to include detailed analysis of egg-specific IgG_4 levels, as well as T-cell cytokine responses. Our results, which are similar to those of other natural history studies,[11-14] are somewhat limited by the fact that OFCs were not performed at protocol-defined intervals in this observational study, with resolution rates therefore likely being conservative estimates, and that many children were deemed egg tolerant based on unsupervised home introductions. Additionally, the study cohort was enrolled based on likely egg or milk allergy without known peanut allergy, which might distinguish this group from other clinical cohorts, although most infants prone to egg allergy would present to allergists with exposure to egg before having ingested peanut.[36] In addition, the reliability of our algorithm might differ if different methods are used for IgE measurements and, ultimately, will require validation in other settings. An additional limitation was that we did not characterize baked egg consumption in a rigorous manner, although approximately a third of those designated as having egg allergy in our cohort reported consumption of products with baked egg without a reaction at 6 years of age. It is important to recognize that our overall estimate of resolution does not include at least some children who might be fully tolerant of even whole forms of egg or whether the introduction of baked egg might have influenced the natural course of egg allergy in this cohort. Nonetheless, the study did not specifically encourage home introduction or OFCs to baked egg products, and therefore we believe the results reflect clinical practice.

In conclusion, we estimate from this well-characterized cohort that approximately 50% of children with egg allergy will become egg tolerant by 6 years of age. Resolution is highly associated with lower egg-specific IgE levels and the absence of systemic reactions beyond the skin on presentation. These highly predictive variables have been used to create a calculator to predict the natural history of egg allergy for individual patients, although additional studies to validate the model will be needed.

Additional site investigators: F. M. Atkins, D. Y. M. Leung, T. T. Perry, and A. M. Scurlock.

Coordinators and support: D. Brown, L. Talarico, S. Noone, K. Mudd, S. Knorr, P. Steele, J. Kamilaris, S. Carlisle, P. Mayfield, M. Mishoe, M. Beksinska, H. Haczynska, J. Grabowska, A. Hiegel, J. Straw, L. Christie, M. Groetch, J. Ellingson, J. Stone, S. Leung, K. Morgan, K. Brown-Engelhardt, and S. Cushing.

We thank Dr Marshall Plaut, the medical officer, and J. Poyser for managing the project for CoFAR (NIAID) and Dr R. Lindblad from EMMES. We thank the families who kindly participated. We thank the staff of the clinical research units at each institution and the statistical and clinical coordinating center, without whose participation the study could not have been done. We thank Greer Laboratories (Lenoir, NC) and Thermo Fisher Scientific (Waltham, Mass) for supplying reagents.

We dedicate this work to our colleague and friend, Lloyd Mayer, MD.

Clinical implications: Egg allergy resolution by school age can be predicted by early clinical manifestations and egg-specific IgE levels.

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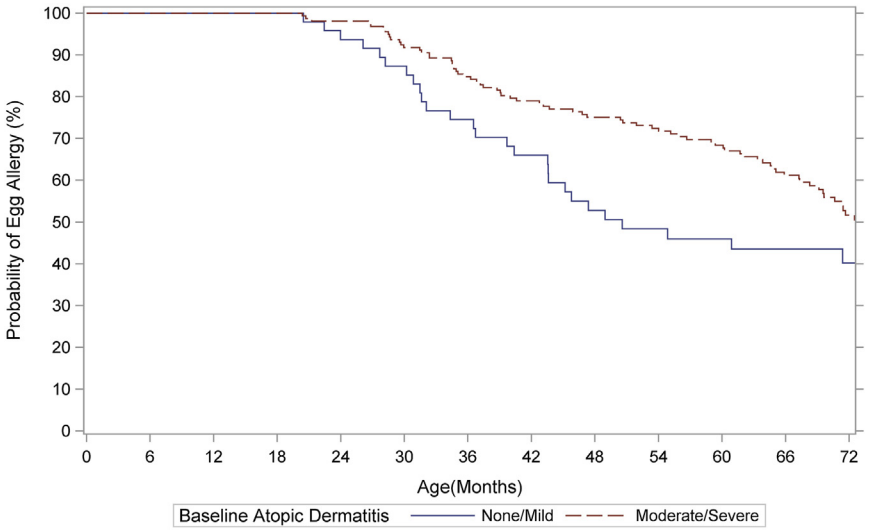

FIG E1. Kaplan-Meier Analysis representing the relationship of egg allergy resolution to baseline AD. Individual curves represent no/mild AD *(blue)* and moderate/severe AD *(red)*.

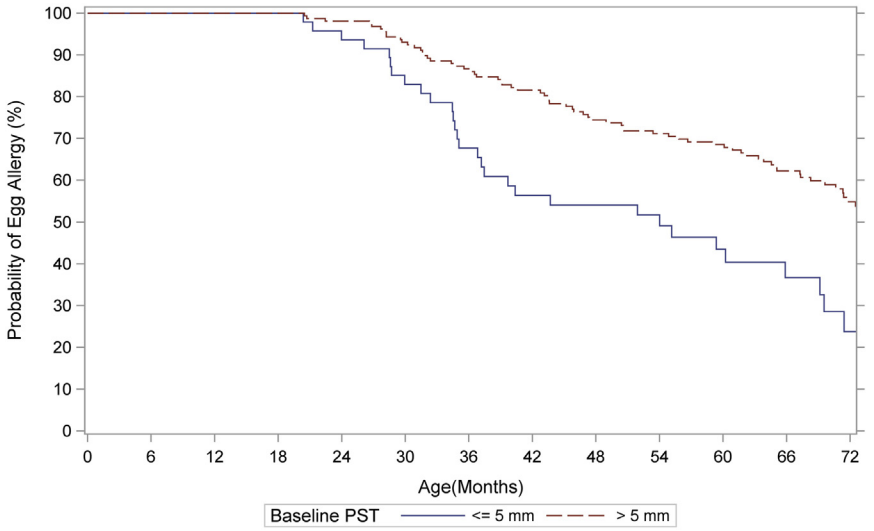

FIG E2. Kaplan-Meier analysis representing the relationship of egg allergy resolution to baseline egg SPT wheal size. Individual curves represent wheal sizes of less than 5 mm *(blue)* or greater than 5 mm *(red)*.

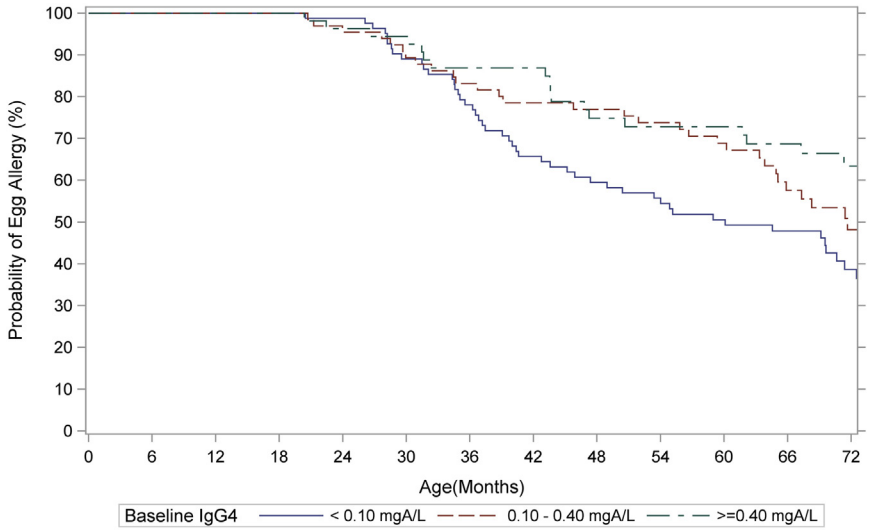

FIG E3. Kaplan-Meier analysis representing the relationship of egg allergy resolution to baseline egg-specific IgG_4 levels. Individual curves represent IgG_4 levels of less than 0.10 mg_A/L *(blue)*, 0.10 to 0.40 mg_A/L *(red)*, and 0.40 mg_A/L or greater *(green)*.

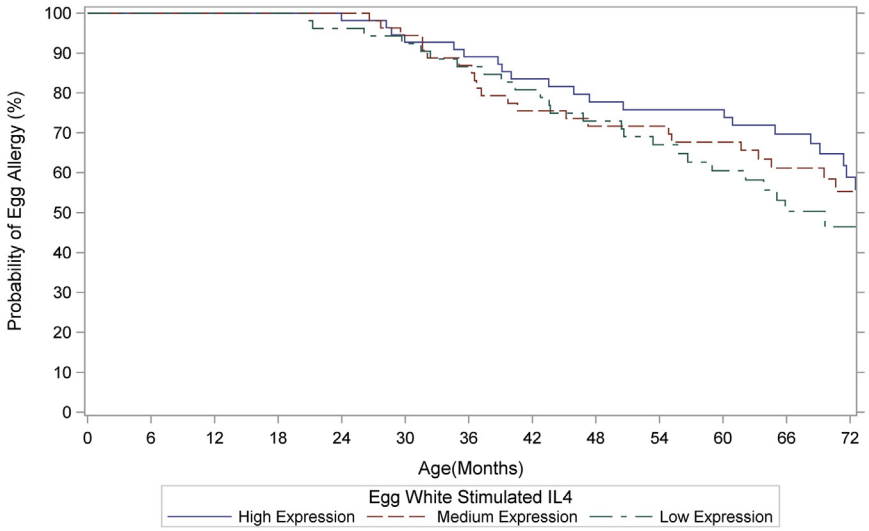

FIG E4. Kaplan-Meier analysis representing the relationship of egg-stimulated IL-4 expression based on observed tertiles of response (high in *red*, medium in *blue*, and low in *green*).

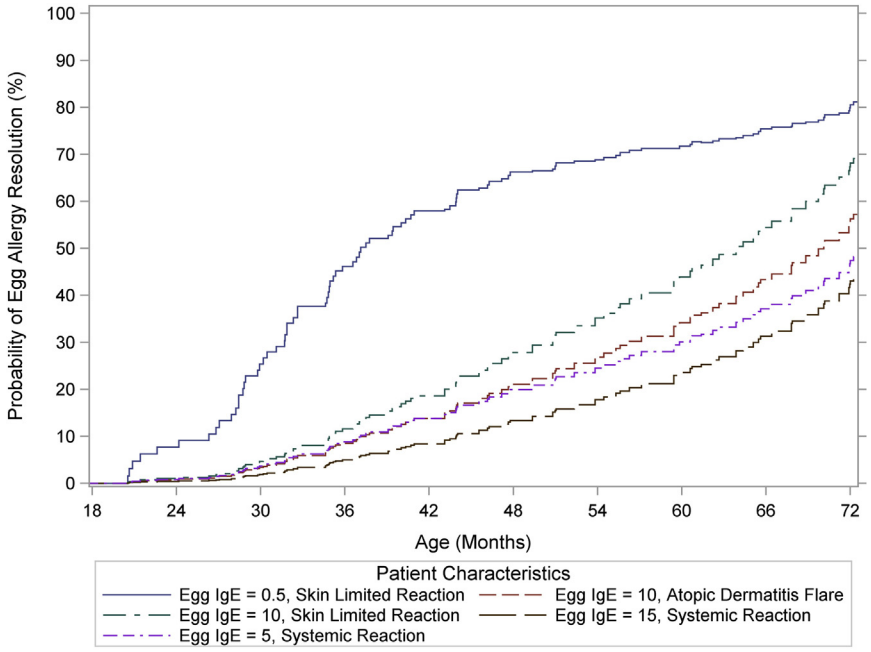

FIG E5. This figure represents results of a composite index based on the baseline egg-specific IgE level and clinical presentation of egg allergy being limited to the skin or including symptoms beyond the skin (see text). Five examples representing common clinical presentations are shown, illustrating systemic reactions with egg-specific IgE levels of 15 kU_A/L *(brown line)* and 5 kU_A/L *(purple),* skin-limited reactions with egg-specific IgE levels of 10 kU_A/L *(green)* and 0.5 kU_A/L *(blue),* and AD with egg-specific IgE levels of 10 kU_A/L *(red).*

TABLE E1. Grading severity of AD (approach derived from Rajka and Langeland)[19]

Factor	Score	Description
Extent*	1	<9% BSA
	2	>9% to 36% BSA
	3	>36% BSA
Course	1	>3 mo remission in past year (>25% lifetime in remission for age <1 y)
	2	<3 mo remission, not continuous (<25% lifetime in remission for age <1 y)
	3	Continuous
Intensity	1	Mild itch, rarely disturbs sleep
	2	Itch more than above, less than below
	3	Severe itch usually disturbs night's sleep

BSA, Body surface area.
*Based on "rule of nines" (age 0-1 years: head, 19%; trunk, 34%; arms, 19%; legs, 26%; age 1-4 years: head, 17%; trunk, 34%; arms, 19%; legs, 30%). Summation scores of 3 to 4 indicate mild disease, scores of 5 to 7 indicate moderate disease, and scores of 8 to 9 indicate severe AD.

TABLE E2. Baseline characteristics by study site

	Site										All	
	National Jewish MRC		Duke University		Johns Hopkins University		Mount Sinai Medical Center		University of Arkansas			
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total subjects	42	100.00	20	100.00	37	100.00	47	100.00	67	100.00	213	100.00
Baseline age (mo)												
3-5	0	0.00	1	5.00	2	5.41	5	10.64	5	7.46	13	6.10
6-8	7	16.67	1	5.00	7	18.92	9	19.15	8	11.94	32	15.02
9-12	14	33.33	11	55.00	15	40.54	18	38.30	30	44.78	88	41.31
13-15	21	50.00	7	35.00	13	35.14	15	31.91	24	35.82	80	37.56
Sex												
Female	11	26.19	4	20.00	11	29.73	13	27.66	24	35.82	63	29.58
Male	31	73.81	16	80.00	26	70.27	34	72.34	43	64.18	150	70.42
Race												
White	34	80.95	16	80.00	27	72.97	43	91.49	41	61.19	161	75.59
Black/African American	2	4.76	2	10.00	4	10.81	2	4.26	26	38.81	36	16.90
Asian	3	7.14	2	10.00	5	13.51	2	4.26	0	0.00	12	5.63
Other	3	7.14	0	0.00	1	2.70	0	0.00	0	0.00	4	1.88
Parental history of atopy												
Missing	2	4.76	0	0.00	0	0.00	1	2.13	2	2.99	5	2.35
Neither parent	4	9.52	4	20.00	6	16.22	9	19.15	10	14.93	33	15.49
One parent	13	30.95	7	35.00	16	43.24	19	40.43	24	35.82	79	37.09
Both parents	23	54.76	9	45.00	15	40.54	18	38.30	31	46.27	96	45.07
Household income												
Missing	3	7.14	6	30.00	2	5.41	13	27.66	5	7.46	29	13.62
<$50,000	10	23.81	3	15.00	3	8.11	2	4.26	37	55.22	55	25.82
$50,000-$99,0000	14	33.33	5	25.00	6	16.22	7	14.89	13	19.40	45	21.13
≥$100,000	15	35.71	6	30.00	26	70.27	25	53.19	12	17.91	84	39.44
Maternal education												
Missing	0	0.00	1	5.00	0	0.00	1	2.13	0	0.00	2	0.94
High school or less	7	16.67	4	20.00	0	0.00	3	6.38	21	31.34	35	16.43
Some college/college degree	15	35.71	7	35.00	15	40.54	22	46.81	34	50.75	93	43.66
Graduate degree	20	47.62	8	40.00	22	59.46	21	44.68	12	17.91	83	38.97
Paternal education												
Missing	0	0.00	2	10.00	0	0.00	1	2.13	0	0.00	3	1.41
High school or less	6	14.29	5	25.00	3	8.11	4	8.51	33	49.25	51	23.94
Some college/college degree	24	57.14	6	30.00	9	24.32	19	40.43	27	40.30	85	39.91
Graduate degree	12	28.57	7	35.00	25	67.57	23	48.94	7	10.45	74	34.74

TABLE E3. Factors affecting resolution of egg allergy among subjects with egg allergy

	Parameter	HR (95% CI)	*P* value
Egg-specific IgE per $\log_{10}$ (kU_A/L)	Baseline	0.11 (0.04-0.31)	<.0001
	Egg-specific IgE by time (mo) interaction	1.03 (1.01-1.05)	.007
Skin reaction classification	Baseline AD vs skin-limited reactions	0.72 (0.36-1.44)	.36
	Baseline systemic vs skin-limited reactions	0.52 (0.34-0.79)	.002